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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/029,905	12/21/2001	Birgit Jung	1/1177	5115

28501 7590 03/30/2004

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EXAMINER	
STEADMAN, DAVID J	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 03/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/029,905	JUNG ET AL.	
	Examiner	Art Unit	
	David J Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8 and 10-54* is/are pending in the application.

4a) Of the above claim(s) *12-15 and 19-54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,10,11 and 16-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *02/05/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] Claims 1-8 and 10-54 are pending in the application.

[2] Applicants' amendment to the claims, filed February 05, 2004, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

Election/Restriction

[3] Applicants' election without traverse of the invention of Group I, claims 1-8, 10-11, and 16-18, filed February 05, 2004, is acknowledged.

[4] Claims 12-15 and 19-54 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

[5] Claims 1-8, 10-11, and 16-18 are being examined on the merits. Claims 1-8 and 16-18 are being examined only to the extent the claims read on the elected subject matter.

Information Disclosure Statement

[6] Receipt of an information disclosure statement, filed February 05, 2004, is acknowledged. It is noted that applicants assert this IDS to be a copy of the IDS filed April 23, 2003. As the examiner could find no list of references in the IDS filed April 23, 2003, the examiner previously requested that applicants submit a list of the references cited therein (see item [2] of the Office action mailed November 04, 2003). All

references cited by applicants in the information disclosure statement (IDS) filed February 05, 2004, have been considered by the examiner. A copy of the IDS is attached to the instant Office action.

Priority

[7] Applicants' claim to domestic priority under 35 USC 119(e) to provisional application 60/257,854, filed 12/22/2000, in the first paragraph of the specification as originally filed is acknowledged. It is noted that SEQ ID NO:4 of the instant application is listed as SEQ ID NO:4 in provisional application 60/257,854. Applicants are granted the benefit of the earlier filing date of 12/22/2000 to the extent provisional application 60/257,854 provides support for the claimed invention.

Sequence Compliance

[8] This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825; applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). To be in compliance, applicants should identify nucleotide sequences of at least 10 nucleotides and amino acid sequences of at least 4 amino acids in the specification by a proper sequence identifier, i.e., "SEQ ID NO:" (see MPEP 2422.01). If these sequences have not been listed in the computer readable form and paper copy of the sequence listing,

applicant must provide an initial computer readable form (CRF) copy of the "Sequence Listing", an initial paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification, and a statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d). See particularly page 26, line 32.

Specification/Informalities

[9] The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: Method for identifying compounds that activate or inhibit PAK2.

Claim Objections

[10] Claims 1-2, 5-6, and 10 are objected to because of the recitation of "DHAM-kinase" and/or "PAK2". Abbreviations, unless otherwise obvious, should not be recited in the claims without at least once reciting the entire phrase for which the abbreviation is used, e.g., "deactivated in hyperactive macrophage kinase" for DHAM-kinase as disclosed at page 6, bottom of the specification. Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

[11] Claim(s) 1-8, 10-11, and 16-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

[a] The methods of claims 1 and 2 (claims 3-8, 10-11, and 16-18 dependent therefrom) are incomplete. The claims are drawn to methods for determining whether a substance is an activator or an inhibitor, however, there is no correlation between method steps (a) and (b) and whether the substance is an activator or inhibitor. It is suggested that applicants incorporate a step which correlates inhibition or activation of DHAM-kinase function to the substance as an activator or inhibitor. For example, by amending the claim to recite step (c): wherein inhibition or activation of DHAM-kinase by the substance is indicative of an inhibitor or activator, respectively, of the protein.

[b] Claims 1-2 (claims 5-8 and 10-11 dependent therefrom) and claims 3-4 are indefinite in the recitation of "function". The specification discloses examples of DHAM-kinase functions, including "enzymatic activity" (page 8, line 18) and "substrate phosphorylation, recognition, and /or binding" (page 7, line 20). However, as these are disclosed as being examples, it is unclear as to the scope of functions that are be encompassed or not encompassed by the term "function". It is suggested that applicants clarify the meaning of the term "function".

[c] Claims 1-2 (claims 3-8 and 16-18 dependent therefrom) are indefinite in the recitation of "PAK2" as the specification fails to teach which identifying characteristics distinguish a "PAK2" from other serine/threonine kinases. The application discloses that

PAK2 is a serine/threonine kinase (page 7, line 3) that has the following characteristics: "preferentially interacts with activated Cdc42 and Rac, but not Rho" which "leads to autophosphorylation of PAK2 and activation of its kinase activity"; "PAK2 can phosphorylate myosin 11, MLCK (myosin light chain kinase), p47phox (NADPH oxidase), and Raf-I"; and "is involved in actin reorganization and cell motility" (page 17, lines 19-24). However, the scope of serine/threonine kinases considered to be encompassed by the term "PAK2" is unclear as the specification fails to define which of these characteristics are necessary for inclusion of a PAK2 kinase which is distinct in sequence from those disclosed to be considered to be within this class. It is suggested that applicants clearly identify those proteins considered to be a "PAK2" protein by, for example, the use of a sequence identifier, e.g., SEQ ID NO:4.

[d] Claims 3-4 are indefinite in the recitation of "measured directly" and "measured indirectly". It is unclear as to how one distinguishes a direct measurement from an indirect measurement and the terms can be interpreted such that a direct measurement to a first skilled artisan can be an indirect measurement to a second skilled artisan and vice versa. Thus, it is unclear as to the scope of measurements that are intended to be direct or indirect. It is suggested that applicants clarify the meanings of the terms.

[e] Claim 10 is confusing as the claim depends (in part) from claim 2, which recites a PAK2 protein that is a "variant, mutant or fragment" of a PAK2 kinase. However, claim 10 limits the PAK2 kinase to consisting of SEQ ID NO:4, which appears to be a full-length wild-type PAK2 and would not be considered to be a variant, mutant, or fragment

of a PAK2 as recited in claim 2. It is suggested that applicants clarify the meaning of the claim.

[f] Claim 11 is confusing as it is unclear as to how the protein recited in claim 10, i.e., "the PAK2 consists of an amino acid sequence of SEQ ID NO:4", can simultaneously be a "variant, mutant or fragment of SEQ ID NO:4" as recited in claim 11. It is suggested that applicants clarify the meaning of the claim.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

[12] Claims 1-8, 11, and 16-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of he claimed invention.

The claims are drawn to methods for determining whether a substance is an activator or an inhibitor of a function of a genus of PAK2 proteins. For claims drawn to a genus, MPEP § 2163 states the written description requirement for a genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying

characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406. MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In this case, the specification discloses only a single representative species of the recited genus of PAK2 proteins, i.e., SEQ ID NO:4. While the specification describes the function of "PAK2" as a "serine/threonine kinase" (page 17, line 19), the genus of recited PAK2 polypeptides encompasses species that are WIDELY variant in their structures, encompassing a vast number of polypeptide structures having serine/threonine kinase activity. As such, the disclosure of the single representative species is insufficient to be representative of the attributes and features of all species encompassed by the claimed genus. Given the lack of description of a representative number of PAK2 polypeptides, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention. Furthermore, specifically regarding claims 5-6, it is noted that the genus of PAK2 proteins is limited to those that are "mammalian" or "human". The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical

species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398 (Fed. Cir. 1997), quoting *Fiers v. Revel* , 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Also, MPEP § 2163 states (citing *Amgen*, 927 F.2d at 1206, 18 USPQ2d at 1021), "A gene is a chemical compound, albeit a complex one, and it is well established in our law that conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials". In this case, the specification fails to provide those characteristics that distinguish a "mammalian" or "human" PAK2 polypeptide from those PAK2 proteins that are not "mammalian" or "human". At least for the reasons stated above, the specification fails to provide adequate written description for the recited genus of PAK2 proteins.

[13] Claim(s) 1-8, 10-11, and 16-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for determining whether a substance is an activator or inhibitor of the kinase activity of SEQ ID NO:4, comprising the following steps: (a) contacting the polypeptide of SEQ ID NO:4 with a test substance in the presence of a substrate of SEQ ID NO:4; and (b) measuring whether phosphorylation of the substrate of SEQ ID NO:4 is inhibited or activated relative to phosphorylation of the substrate in the absence of the test substance, does not reasonably provide enablement for a method for determining whether a substance is an activator or inhibitor of <u>any</u> function of <u>all</u> PAK2 proteins, including variants, mutants, and fragments thereof, comprising the steps: (a) contacting the PAK2 protein; and (b)

measuring whether any function of the PAK2 protein is inhibited or activated. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

It is the examiner's position that undue experimentation would be required for a skilled artisan to make and/or use the entire scope of the claimed invention. Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). The Factors most relevant to the instant rejection are addressed in detail below.

- The claims are overly broad in scope: The claims are so broad as to encompass for a method for determining whether a substance is an activator or inhibitor of any function of all PAK2 proteins, including variants, mutants, and fragments thereof, comprising the steps: (a) contacting the PAK2 protein; and (b) measuring whether any function of the PAK2 protein is inhibited or activated. The broad scope of claimed methods is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of PAK2 proteins, functions thereof, and methods

of measuring said functions. In this case the disclosure is limited to a method for determining whether a substance is an activator or inhibitor of the kinase activity of SEQ ID NO:4, comprising the steps: (a) contacting the polypeptide of SEQ ID NO:4 with a test substance in the presence of a substrate of SEQ ID NO:4; and (b) measuring whether phosphorylation of the substrate of SEQ ID NO:4 is inhibited or activated relative to phosphorylation of the substrate in the absence of the test substance.

- The lack of guidance and working examples: The specification provides two working examples of the claimed methods, which both involve the measurement of SEQ ID NO:4 kinase activity (see pages 24-27 of the instant specification). These working examples fail to provide the necessary guidance for making the entire scope of claimed methods, particularly with respect to the broad scope of recited PAK2 polypeptides, functions thereof, and methods of measuring said functions. Regarding the variants, mutants, and fragments of PAK2 or SEQ ID NO:4, it is noted that the specification fails to provide guidance regarding those amino acids of all PAK2 proteins or SEQ ID NO:4 that may be altered by substitution, deletion or insertion with an expectation of maintaining the desired activity and further fails to identify an active site of all PAK4 proteins or SEQ ID NO:4 such that one of skill in the art can use a fragment of the recited proteins to practice the claimed methods.

- The high level of unpredictability in the art: The amino acid sequence of a given polypeptide determines the protein's structural and functional properties. Predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids

in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e., expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. The positions within a protein's sequence where modifications can be made with a reasonable expectation of success in obtaining an encoded polypeptide having the desired activity/utility are limited in any protein and the result of such modifications is highly unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions. In this case, the necessary guidance has not been provided in the specification as explained above.

- The state of the prior art supports the high level of unpredictability: The state of the art provides evidence for the high degree of unpredictability in altering the amino acid sequence of a polypeptide with an expectation that the polypeptide will maintain the desired activity/utility. For example, Branden et al. ("Introduction to Protein Structure", Garland Publishing Inc., New York, 1991) teach "[p]rotein engineers frequently have been surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes" and "[t]he often surprising results of such experiments reveal how little we know about the rules of protein stability... ...they also serve to emphasize how difficult it is to design *de novo* stable proteins with specific functions" (page 247). While it is acknowledged that this reference was published in 1991, to date there remains no certain method for reasonably predicting the effects of even a *single* amino acid mutation on a protein.

- The amount of experimentation required is undue: While methods of measuring the kinase activity of a given serine/threonine kinase are known, it is not routine in the art to make all PAK2 proteins, variants, mutants, and fragments thereof having kinase activity or variants, mutants, or fragments of SEQ ID NO:4 having kinase activity and to determine all methods by which any function of said proteins can be measured to identify an activator or inhibitor substance as encompassed by the instant claims. Thus, in view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, and the high degree of unpredictability as evidenced by the prior art, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention.

Thus, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

[14] Claim(s) 1-6, 8, 10-11, and 16-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Benner et al. (J Biol Chem 270:21121-21128) as evidenced by Database GenPept Accession Number Q13177. The claims are drawn to methods for determining whether a substance is an activator or an inhibitor of a function of PAK2.

Benner et al. teach methods for assaying the effects of trypsin and magnesium on the activity of a kinase, referred to as S6/H4 kinase or PAK 65 (page 21122, left column). Benner et al. teach that addition of trypsin to the full length kinase cleaves the holoenzyme, which has minimal enzymatic activity, thereby generating a fully active enzyme (page 21122, left column). Benner et al. also teach the addition of magnesium to a reaction buffer activates the kinase activity of both the full length and trypsin-cleaved forms of the kinase (see page 21122, left column).

Database GenPept Accession Number Q13177 teaches that S6/H4 kinase and PAK 65 are synonymous with PAK2 and cite the reference of Benner et al., indicating that the protein disclosed in the reference of Benner et al. uses a protein having the sequence disclosed in Database GenPept Accession Number Q13177. A sequence alignment of the kinase disclosed in Database GenPept Accession Number Q13177 is

100% identical to SEQ ID NO:4 of the instant application (see attached sequence alignment). This anticipates claims 1-6, 8, 10-11, and 16-18 as written.

[15] Claim(s) 1-8, 11, and 16-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Lee et al. (PNAS 94:13642-13647). The claims are drawn to methods for determining whether a substance is an activator or an inhibitor of a function of PAK2.

Lee et al. teach a method for assaying the effects of Fas-induced apoptosis and caspase cleavage on the activation of human PAK 65/PAK2 and a deletion fragment thereof (page 13643, left column). This anticipates claims 1-8, 11, and 16-18 as written.

Conclusion

[16] Status of the claims:

- Claims 1-8 and 10-54 are pending.
- Claims 12-15 and 19-54 are withdrawn from consideration.
- Claims 1-8, 10-11, and 16-18 are rejected.
- No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (571) 272-0942. The Examiner can normally be reached Monday-Friday from 7:00 am to 5:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (571) 272-0928. The FAX number for submission of official papers to Group 1600 is (703) 308-4242. Draft or informal FAX communications should be directed to (571) 273-0942. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman, Ph.D.
Patent Examiner
Art Unit 1652
03-26-04